PEPTIC ULCER AND CHRONIC RENAL FAILURE

by

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PROBABLY the first real attempt to ascertain if any casual relationship existed between peptic ulcer and renal disease was contained in a survey of post mortem records by Perry and Shaw (1893). They found that some form of kidney disease was present in seven per cent of deaths and as their cases of duodenal ulcer numbered 70, they reasoned that seven per cent, or five cases, might have been expected to have coincident Bright's disease. In fact, 12 cases showed this association and they concluded that "there appears to be some reason for including Bright's disease as one of the predisposing causes of duodenal ulcer". Moynihan in his classical textbook on duodenal ulcer (1910) described 27 autopsy cases where ulceration affecting the duodenum was associated with an advanced pathological condition of the kidneys, and he hinted at an association between the two diseases. Thereafter the subject received little further attention until the early 1960s when attempts were made to prolong the lives of uraemic patients by regular dialysis and transplantation. Subsequently, peptic ulcer was recognised as a serious complication in uraemic patients receiving regular dialysis (Sokol, 1964), and in those undergoing kidney transplantation (Moore and Hume, 1969). In some centres, the incidence of upper gastrointestinal haemorhage and perforation following transplantation was so high it was even suggested that all uraemic patients should have vagotomy carried out prior to transplantation (Penn et al., 1968).

In the present study, gastric function has been examined in 186 patients undergoing treatment for chronic renal failure, including patients on dialysis and following renal transplantation. The study attempted to answer several questions. Is peptic ulcer commoner in chronic renal failure? Is gastric acid secretion affected by chronic uraemia, dialysis and transplantation? And do gastrointestinal hormones have a role to play? Finally it was hoped the study might provide guidelines for management of peptic ulcer disease in these patients.

PATIENTS AND METHODS

Of the patients studied 131 had a barium meal, and 106 had a pentagastrin test under standard conditions carried out by the same experienced personnel. Endoscopy usually including fundal biopsy, was carried out on 26 patients who had either gastro-intestinal bleeding or x-ray negative dyspepsia. Radioimmunoassay of the following gastrointestinal hormones was carried out in the fasting state and after a standard meal: gastrin, glucagon, (measured as total glucagon or N-terminal glucagon-like immunoreactivity (N-GLI) and pancreatic glucagon or C-terminal glucagon-like immunoreactivity (C-GLI)) vasoactive intestinal peptide (VIP), secretin and insulin. The techniques involved in these hormone assays have been described in full elsewhere (Buchanan 1973).

Patients studied included 100 patients with advanced renal failure (Creatinine clearance less than 10 ml/min); 31 patients undergoing regular haemodialysis therapy, most with negligible renal function (creatinine clearance less that 3 ml/min); 55 patients with functioning cadaver kidney grafts, studied three to 140 months after transplantation, all of whom were receiving azathioprine and prednisolone.

Statistical methods used were the Student t test for analysis of radioimmunoassay data, the non-parametric Mann-Whitney 'U' test for acid secretory data which was not normally distributed, and linear regression analysis with calculation of partial correlation coefficients.

RESULTS

Peptic Ulcer

Table 1 shows the results of gastric assessment in 131 uraemic patients. Of 100 patients with advanced chronic renal failure (CRF) examined by barium meal, 18 of 70 males had an ulcer crater or scar (26 per cent) and 1 of 30 females (3 per cent), a total frequency of 19 per cent. Of 31 patients receiving regular dialysis therapy (RD) and examined by both barium meal and endoscopy, 12 of 20 males had an ulcer crater or scar (60 per cent) and 3 of 11 females (27 per cent), a total frequency of 48 per cent. Thus 34 (26 per cent) of 131 CRF and RD patients had peptic ulcer disease. Of these 34 only one patient had a gastric ulcer, all the rest suffered duodenal ulceration (13 had ulcer craters, 20 had chronic scarring).

TABLE 1

Upper gastrointestinal tract findings in 131 patients with advanced uraemia. (CRF—chronic renal failure; RD—regular dialysis)

Group	*No. of Patients*	*Method of Investigation*	*No. with Ulcer Disease (%)*
CRF	100 (70 Male (30 Female	Radiology	19 Male and Female (19%)
			18 Male (26%)
			1 Female (3%)
RD	31 (20 Male (11 Female	Radiology/Endoscopy	15 Male and Female (48%)
			12 Male (60%)
			3 Female (27%)

Gastric Acid Secretion

Table 2 shows the results of basal and peak acid output (PAO) in 106 patients undergoing treatment for chronic renal failure and in 24 normal subjects. There was no significant difference in mean age (Student t test) or sex distribution (chi-squared

test) between controls and any of the three groups studied. The table shows the results for acid secretion in males and females combined, but the results were similar when the sexes were examined separately.

TABLE 2

*Basal and peak acid output in patients with chronic renal failure (CRF), undergoing regular dialysis (RD) and following renal transplantation (RT). (*compared with controls)*

		Basal Acid Output mmol/hr.			*Peak Acid Output mmol/hr.*		
Group	*No. of Subjects*	*Median*	*Range*	*P**	*Median*	*Range*	*P**
Controls	24	1.2	0—5.5		19.8	0.8—44.8	
C.R.F.	32	2.2	0—9.3	<0.1	22.0	0—51.0	<0.1
R.D.	36	3.6	0—12.1	<0.01	33.1	0—78.0	<0.02
R.T.	38	2.4	0.1—11.4	<0.05	31.9	6.2—69.0	<0.01

Table 3 shows the percentage of hyposecretors (PAO$<$10 mmol/hr) and hypersecretors (PAO$<$30 mmol/hr in females, $<$45 mmol/hr in males) in each group; Figure 1 illustrates individual values for PAO in the four groups, and Figure 2 shows the relationship between PAO and time elapsed post-transplant in the group of 38 renal transplant (RT) patients. Calculation of partial correlation coefficients showed that the negative correlation between PAO and time elapsed post-transplant remained significant ($P<0.02$) after controlling for the influence of age, and that there was no independent relationship between PAO and prednisolone dosage.

TABLE 3

Percentage of hypo—and hypersecretors

Group (Male and Female)	*Hyposecretion*	*Hypersecretion*
Chronic Renal Failure (32)	22%	3%
Regular Dialysis (36)	22%	42%
Renal Transplant (38)	8%	29%

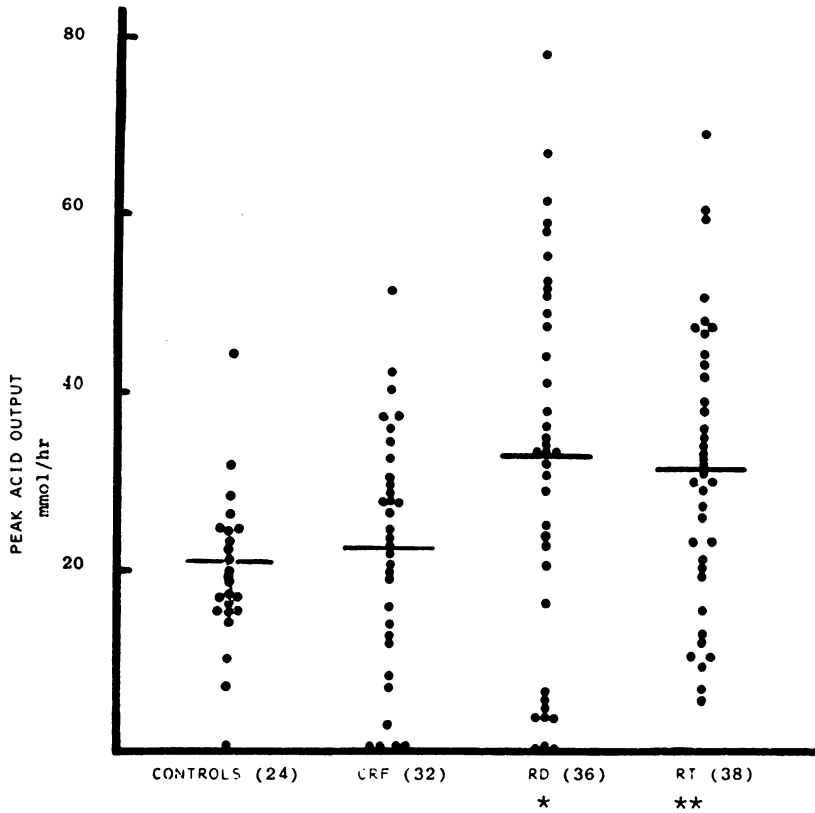


FIGURE 1

*Peak acid output (PAO) in CRF, RD and RT patients compared with normal subjects (*P<0.02, **P<0.01)*

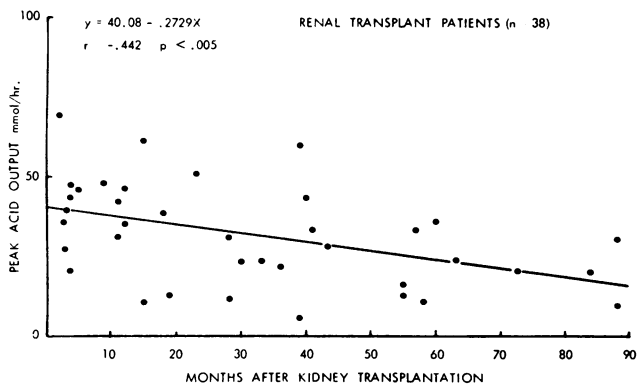


FIGURE 2

Relationship of peak acid output (PAO) and time post-transplant in 38 RT patients

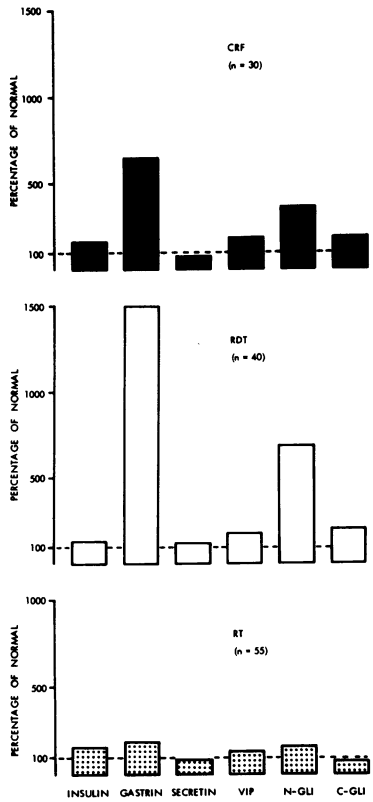


FIGURE 3
Fasting plasma levels of gastrointestinal hormones

Gastrointestinal (GI) Hormones

Figure 3 shows fasting plasma levels of several GI hormones in uraemic patients undergoing dialysis and transplantation, and Figure 4 the effect of a standard mixed meal on plasma gastrin levels in these patients compared with normal subjects. Figure 5 illustrates the influence of hypochlorhydria on fasting plasma gastrin in uraemic patients, and Figure 6 the relationship between plasma gastrin and PAO in RD patients when those with hypochlorhydria are excluded.

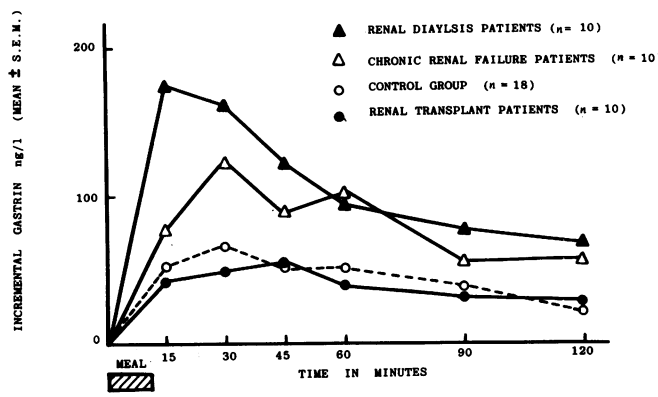


FIGURE 4
Food-stimulated plasma gastrin response

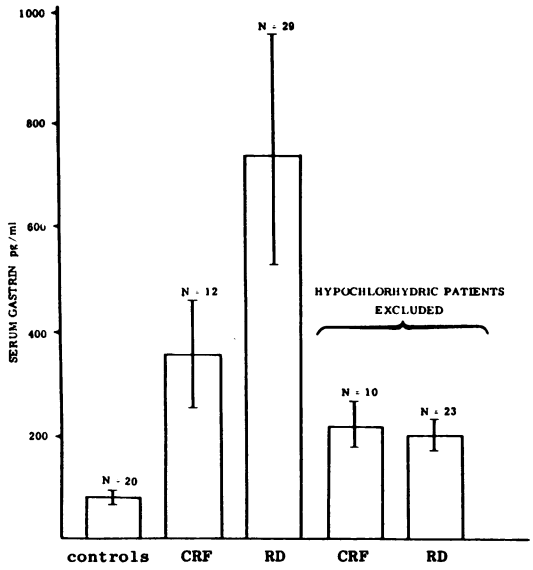
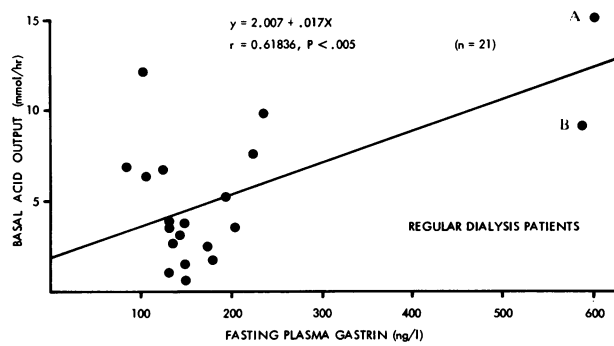


FIGURE 5
The mechanism of hypergastrinaemia in uraemia: role of hypochlorhydria

FIGURE 6
Relationship between fasting plasma gastrin and peak acid output in RD patients (excluding those with hypochlorhydria). Patients A and B had particularly severe ulcer disease (see text).



DISCUSSION

It appears that peptic ulcer is unusually frequent in patients undergoing treatment for chronic renal failure, 34 (26 per cent) of 131 such patients in this study showing either an ulcer crater or scar. Figures were highest (48 per cent) in those undergoing regular dialysis and assessed by radiology and endoscopy, and there was a marked predominance of duodenal ulceration. Other authors have studied the occurrence of peptic ulcer in advanced uraemia but in a review of 19 series comprising a total of 910 uraemic patients (Doherty, 1978) only 97 patients (11 per cent) had peptic ulcer proven by surgery, autopsy or barium meal. However only 145 of these 910 patients were receiving regular dialysis, and 45 (31 per cent) of this group had peptic ulceration. Coarsening of mucosal pattern on the barium meal was remarked upon in several of the studies reviewed, and noted to be a very common feature (65 per

cent in one series). Explanations put forward included mucosal oedema due to hypoproteinaemia (Weiner, Vertez and Shapiro, 1969) and hypertonicity of the muscularis mucosae due to irritation from uraemic gastritis. Connell (1973), in discussing the significance of coarse mucosal folds, states that they are associated with gastric acid hypersecretion and are seen in a high proportion of cases with duodenal ulceration. Patients with x-ray negative dyspepsia who have coarse gastric folds are more likely to have surgery subsequently than patients with normal folds (Krag, 1965). In practice, enlarged mucosal folds can produce deep clefts which may make it difficult to exclude an ulcer niche, and the high frequency of ulcer in the present study may perhaps be due to use of combined radiology and endoscopy.

It is difficult to find reliable figures for the prevalence of ulceration in a non-uraemic population for the purpose of comparison with the patients in this study. Doll and Jones (1951) surveyed a healthy population of 6,047 subjects drawn from the London area and reported the occurrence of ulcer to be 6.4 per cent in men and 1.7 per cent in women. However, they carried out barium meals only on patients giving a history of dyspepsia, whereas all patients in the present study had a barium meal examination. A post-mortem study by Watkinson (1958) estimated that one in six men over the age of 35 had suffered from ulcer at some time, as did one in eight women. Patients in the present study were younger than the subjects of these surveys, and as the prevalence of ulcer increases with age it seems highly probable that there is a real increase in frequency of peptic ulceration in chronic renal failure, especially in patients undergoing regular dialysis.

It is logical therefore to assume that some underlying mechanism connects the two diseases. Explanations suggested have included the psychological stress associated with haemodialysis (Sokol, 1964), secondary hyperparathyroidism (Gingell, 1968) and Chisholm, 1968) and impairment of pancreatic exocrine function (Bartos, Melichar and Erben, 1970). Table 2 shows the results of acid output measured by pentagastrin stimulation in patients with chronic renal failure (CRF), undergoing regular dialysis (RD) and following renal transplantation (RT). While the results are in keeping with the traditional concept of uraemic hypoacidity (22 per cent in the group studied here) they showed that in uraemic patients treated by regular dialysis, gastric acid secretion is in fact greater than in normal subjects (Figure 1) suggesting that acid hypersecretion plays an important role in the association of the two diseases. Why is hypersecretion only apparent in uraemic patients who receive regular dialysis treatment? This is perhaps because dialysis lowers blood urea levels and improves uraemic gastritis, both factors known to influence gastric pH (Von Korff, 1951, Cheli and Dodero, 1958).

What then is the cause of the acid hypersecretion? A possible explanation is found in the effect of renal transplantation on gastric acid output. It is possible that the decline in acid output following renal transplantation (Figure 2) reflects gradual reduction in prednisolone dosage. However, the effect of coricosteroids on gastric secretion is very small (Cooke, 1967) and furthermore, no independent relationship existed between PAO and prednisolone dosage in the patients studied here. Alternatively, as PAO may be considered a measure of parietal cell mass (Card and Marks, 1960), it is reasonable to assume that many patients with advanced uraemia have gastric hyperplasia which subsequently regresses following transplantation.

This phenomenon could represent the effect of associated changes in plasma gastrin, a polypeptide hormone with a trophic effect on gastric mucosa (Johnston, 1974) and dependent in large part on the kidney for removal from the circulation (Clendinnen et al, 1971). Figure 3 illustrates that gastrin levels are significantly elevated in uraemic patients and return towards normal after renal transplantation.

A large number of other gastro-intestinal hormones are known to affect acid secretion and although the physiological role of many awaits clarification, recent studies indicated secretin may be involved in peptic ulceration (Bloom and Ward, 1975) and also that glucagon and insulin merit further consideration (Hansky and Korman, 1973). Figure 3 shows the levels of these hormones in uraemic patients compared to normal subjects. A deficiency of hormones with acid inhibitory activity (such as secretin) could conceivably lead to acid hypersecretion but such a deficiency is not apparent from the data here. It would appear, therefore, that elevated gastrin levels are the most important hormonal factor in the high acid output of these patients.

In Figure 4 the food stimulated gastrin response in uraemic patients is compared with that of normal subjects. It shows that the rise in circulating gastrin after a meal is greater and more prolonged in CRF and in RD patients, while patients with transplants behave similarly to the normal control group.

It is difficult, however, to relate plasma gastrin levels in uraemic patients to measurements of gastric acid secretion. Figure 5 illustrates that hypochlorhydria contributes to elevation of plasma gastrin levels in uraemic patients, and that the elevation is of lesser degree among patients with normal or increased acid secretion. Although there was a relationship between plasma gastrin and acid output in the RD group from which hypochlorhydric patients were excluded (Figure 6), it is obvious that the correlation is unduly biased by patients A and B. However, it is interesting that both these patients had a form of ulcer disease resembling the Zollinger-Ellison syndrome in severity. It is possible, therefore, that circulating gastrin influences resting acid output in RD patients, but study of greater numbers of patients is necessary to clarify this point.

Upper gastrointestinal complications account for 7.5 per cent of deaths following renal transplantation (Gurland, 1973), and the frequency of ulcer in this study emphasises the importance of pre-operative gastric assessment. The decline in acid output following transplantation suggests that prophylactic vagotomy is unnecessary for uncomplicated ulcer, while favourable preliminary results with cimetidine in patients undergoing dialysis (Doherty et al, 1977) and following transplantation (Doherty et al, 1979) suggest it may prove a suitable alternative.

SUMMARY

Duodenal ulcer is commoner in patients with chronic renal failure especially in those receiving regular dialysis and gastric acid hypersecretion appears to have an important role which may be (in part at least) hormonally mediated. There are abnormal levels of several circulating hormones of the gastro-intestinal tract, of which gastrin appears to be the most important. This hormone may directly influence resting acid secretion and may indirectly affect stimulated acid secretion by a trophic effect on gastric mucosa. Successful renal transplantation tends to

return abnormal gastric function in these patients towards normal. These findings are relevant to the treatment of peptic ulcer in uraemic patients and the prevention of upper gastrointestinal complications after renal transplantation.

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